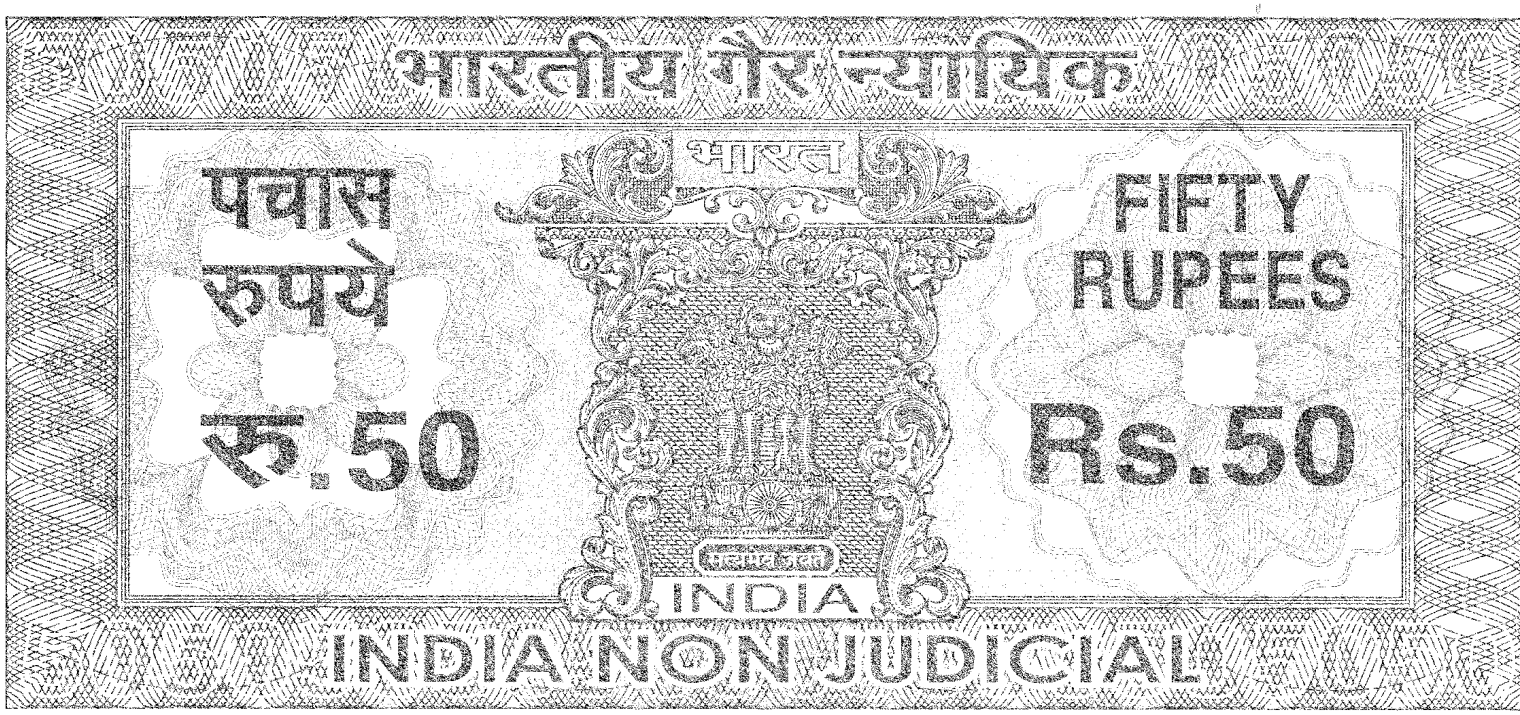

ગુજરાત GUJARAT M 864841

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તારીખ.....૬.....માર્ચ.....સને ૨૦૧૦

નામ :

સરનામું :

દિનેશકુમાર વાસુદેવભાઈ ત્રિવેદી

લા.નં.:-એસ.બી.-૬૩/૧૯૮૬

અમદાવાદ-સીટી સીવીલ કોર્ટના સામંદી

લેનારની સહી X :V.M.Khan

M/S. CADILA HEALTHCARE LTD.
SURVEY NO. 396 - 403
NR. NOVA PETRO CHEMICALS
VILLAGE : MORAIYA,
TALUKA : SANAND.

Rule 132: Declaration of Dr. Bipin Pandey

Commissioner for Patents
P.O Box 1450
Alexandria, VA 22313-1450

Sir,

I, Dr. Bipin Pandey of Cadila Healthcare Limited, Zydus Tower, Satellite Cross Road, Ahmedabad-380 015, Gujarat, India declare the following:

1. I earned a PhD degree in Organic Chemistry from Indian Institute of Technology, Kanpur, India in 1980. Subsequently I was a postdoctoral fellow at Purdue University U.S.A (1981-1983) and an Alexander von Humboldt Foundation Fellow Max Planck Institute, Mulheim, Germany (1983-1985). I continued as Max Plank Society Fellow at Max Planck Institute, Mulheim, Germany. I was senior level scientist at National Chemical Laboratory, Pune (1986-1994), a National Laboratory of Government of India. In the meantime I was a Visiting Scholar at University of California, Berkeley, U.S.A (1990-1992). From last 16 year (1994 onwards), I am a senior level Scientist in Industry starting from Ranbaxy, Sun Pharma Advanced Research Centre (SPARC) and now in Cadila Healthcare Ltd.
2. I am employed as Vice-President at Zydus Research Centre, Cadila Healthcare Limited, Satellite Cross Road, Ahmedabad-380 015, Gujarat, India. I have held that position for the past 09 years. I was also employed as General Manager, Organic Synthesis at Sun Pharma Advanced Research Centre (SPARC) from 1997 to 2000 and Assistant Director, Chemical Research Division, Ranbaxy Research Laboratories, Delhi from 1994 to1996.
3. I have been an author of more than 50 publications in Organic/ Pharmaceutical Chemistry.
4. I am an inventor of this patent application.
5. I have read this patent application and the pending claims, which describes the claimed invention: i.e., preparation of form 1of (S)-(+) clopidogrel bisulfate.
6. On information and belief, I understand that the invention described in this patent application is related to form 1 Clopidogrel bisulfate, which is characterized by its purity, melting point and crystal structure, including XRD.
7. On information and belief, I understand that claims directed to preparation of form 1 of (S)-(+)- Clopidogrel bisulfate were rejected because the Examiner concluded that the product(s) prepared by the claimed process are not adequately described.
8. It is my opinion that the Examiner's rejection is improper because this patent application, as confirmed by the results presented below, does describe making

and using the claimed process and the product(s) prepared by the process. The facts and reasoning on which my opinion is based are discussed below.

9. I have performed the various experiments, which shows the data for the melting point and purity of the Clopidogrel bisulfate form 1. The experiments for (S)-(+)-Clopidogrel Bisulfate Form 1 are:

Experiment No.1

In a round bottom flask, (530 gm) Clopidogrel base was taken in 2500 ml decanol. The reaction mixture was stirred at 50 °C for 10 minutes to obtain a clear solution. Cool the reaction mass to 20 °C; subsequently add 10 ml water and 5 gm of clopidogrel hydrogen sulfate form 1. Sulphuric acid solution (145 gm) was added to reaction mass dropwise at 10-15 °C within 10-15 minutes. A gel type reaction mass was obtained. Warm the reaction mass to room temperature. The reaction mass was stirred for 6.5 hour, washed with methyl tert butyl ether and dried. A solid white Clopidogrel bisulfate form 1 is obtained.

Yield: 565 gm (86.55 %), HPLC purity: 99.77%, Chiral purity: 99.64% (S) Form 1

Melting point: 178-180°C.

XRD- Complies with diffractogram of standard Form 1 of Clopidogrel bisulfate and represented as Fig. 1.

Experiment No. 2

In a round bottom flask, (104.5 gm) Clopidogrel base was taken in 500 ml dodecanol. The reaction mixture was stirred at 50 °C for 10 minutes to obtain a clear solution. Cool the reaction mass to 20 °C; subsequently add 10 ml water and 5 gm of clopidogrel hydrogen sulfate form 1. Sulphuric acid solution (29 gm) was added to reaction mass dropwise at 10-15 °C within 20-30 minutes. A gel type reaction mass was obtained. Warm the reaction masss to room temperature. The reaction mass was stirred for 6.5 hour, washed with methyl tert butyl ether and dried. A solid white Clopidogrel bisulfate form 1 is obtained.

Yield: 118 gm (90%), HPLC purity: 99.47%, Chiral purity: 99.70% (S) Form 1

Melting point: 178-180 °C.

XRD- Complies with diffractogram of standard Form 1 of Clopidogrel bisulfate and represented as Fig. 2.

Experiment No.3

In a round bottom flask, (1 Kg) Clopidogrel base was taken in 5 liter of hexanol. The reaction mixture was stirred at 50 °C for 10 minutes to obtain a clear solution. Cool the reaction mass to 10-15 °C; subsequently add 20.58 ml of water. Sulphuric acid solution (296 gm) was added to reaction mass dropwise at 10-15 °C within 95 minutes. Warm the reaction mass to room temperature. The reaction mass was stirred for 24 hour, washed with methyl tert butyl ether and dried. A solid white Clopidogrel bisulfate form 1 is obtained.

Yield: 1.179 Kg (90 %), HPLC purity: 99.81 %, Chiral purity: 99.45 % (S) Form 1

Melting point: 182-186 °C.

XRD- Complies with diffractogram of standard Form 1 of Clopidogrel bisulfate and represented as Fig. 3.

Comparative Data for the (S)-(+)-Clopidogrel Bisulfate Form 1

Exp.No.	Solvent	Melting Point in °C	HPLC Purity %	Chiral Purity % (S) Form 1	XRD
1	Decanol	178-180 °C	99.77%,	99.64%.	Complies with diffractogram of standard Form 1 of (S)-(+)-Clopidogrel bisulfate Fig. 1
2	Dodecanol	178-180 °C	99.47%.	99.70%.	Complies with diffractogram of standard Form 1 of (S)-(+)-Clopidogrel bisulfate Fig. 2
3	Hexanol	182-186 °C	99.81%.	99.45%.	Complies with diffractogram of standard Form 1 of Clopidogrel bisulfate Fig. 3

10. My results are showing the relationship between the melting point and chiral purity. The melting point, chiral purity and Chemical purity are interlinked. The melting point goes up, if chiral purity is compromised. In fact, melting point can go up to 200°C, if S: R is approx 80:20 (wherein S and R represent the nomenclature of chiral centers according to Cahn-Ingold-Prelog priority rules).
I am also providing some experiments (Experiment No.4 & 5), which show that where the chiral purity is decreased, increase in melting point of Form 1 (S)-(+)-Clopidogrel Bisulfate is observed.

Experiment No.4

In a round bottom flask, (2.2 gm) Clopidogrel base was taken in 9 ml of isopropanol. The reaction mixture was stirred to obtain a clear solution. Cool the reaction mass to 20 °C; subsequently add 0.83 gm sulphuric acid solution (0.74 gm H_2SO_4 + 0.09 gm D.M water) to reaction mass dropwise at 19-20 °C within 7 minutes. Filter the product and dried. A solid white Clopidogrel bisulfate form 1 is obtained.

Yield: 1.3 gm (45 %), Chiral purity: 91.41 % (S)-(+)-Clopidogrel Bisulfate Form 1, Melting point: 205-208 °C.

XRD- Complies with diffractogram of standard Form 1 of (S)-(+)-Clopidogrel bisulfate and represented as Fig. 4.

Experiment No.5

In a round bottom flask, (24gm) Clopidogrel base was taken in 96 ml of isopropanol. The reaction mixture was stirred to obtain a clear solution. Cool the reaction mass to 20 °C; subsequently add 8.94 gm sulphuric acid solution (8.03 gm H_2SO_4 + 0.9 gm D.M water) to reaction mass dropwise at 19-20 °C within 22 minutes. Filter the product and dried. A solid white Clopidogrel bisulfate form 1 is obtained.

Yield: 24.6 gm (78.94 %), Chiral purity: 19.56 % (S)-(+)-Clopidogrel Bisulfate Form 1,Melting point: 205-212 °C.

XRD- Complies with diffractogram of standard Form 1 of (S)-(+)-Clopidogrel bisulfate and represented as Fig.5.

Comparative Data for the (S)-(+)-Clopidogrel Bisulfate Form 1

Exp.No.	Solvent	Melting Point in °C	Chiral Purity % (S) Form 1	XRD
4	Isopropanol	205-208 °C	91.41%.	Complies with diffractogram of standard Form 1 of (S)-(+)-Clopidogrel bisulfate Fig. 4
5	Isopropanol	205-212 °C	19.56%.	Complies with diffractogram of standard Form 1 of (S)-(+)-Clopidogrel bisulfate Fig. 5

Our experiment (Experiment No. 1,2 & 3) shows that we have chemical and chiral purity of (S)-(+)-Clopidogrel Bisulfate Form 1 of more than 99.45 %.

11. The above-described experiments demonstrate that the claimed process prepares (S)-(+)-Clopidogrel bisulfate form 1 having the following characteristics:

Experiment No.1:

HPLC purity: 99.77%, Chiral purity: 99.64%. Melting point: 178-180°C.

XRD 2 θ value (± 0.2): 9.040, 10.720, 11.390, 13.680, 14.210, 14.680, 15.080, 15.340, 16.150, 17.760, 18.090, 18.320, 19.510, 20.420, 21.400, 21.720, 22.440, 23.040, 23.710, 24.290, 24.950, 25.330, 25.790, 26.420, 27.090, 27.270, 28.340, 28.770, 30.620, 31.170, 32.820, 34.540, 34.540, 34.740, 35.370, 36.000, 36.860.

Characteristic d value (°A): 9.77, 3.45, 3.85, 3.74, 4.34, 8.24, 4.83, 3.85, 5.87, 4.99.

Experiment No.2:

HPLC purity: 99.47%, Chiral purity: 99.70%, Melting point: 178-180 °C.

XRD 2 θ value (± 0.2): 9.199, 10.880, 11.520, 13.820, 14.341, 14.800, 15.240, 15.480, 16.300, 17.921, 18.460, 18.959, 19.641, 20.561, 21.561, 21.841, 22.597,

23.179, 23.839, 24.421, 25.021, 25.501, 26.540, 27.419, 28.461, 28.901, 30.760, 31.323, 32.940.

Characteristic d value (°A): 9.60, 3.49, 3.83, 3.72, 4.31, 8.12, 4.80, 3.93, 5.80, 4.94.

Experiment No.3:

HPLC purity: 99.81 %, Chiral purity: 99.45 %, Melting point: 182-186 °C.

XRD 2 θ value (± 0.2): 9.240, 10.930, 11.590, 13.890, 14.400, 14.870, 15.260, 15.530, 16.350, 17.980, 18.280, 18.510, 19.010, 20.610, 21.580, 21.900, 22.660, 23.220, 23.890, 24.520, 25.140, 25.530, 25.970, 26.640, 27.300, 27.470, 28.480, 28.960, 30.780, 31.320, 32.640, 32.960, 36.580.

Characteristic d value (°A): 9.56, 3.48, 3.82, 3.72, 4.30, 8.08, 4.84, 3.92, 5.80, 4.92.

12. Therefore, I conclude that the specification of this patent application adequately describes how to make and use the claimed process and its preparation of form 1 of (S)-(+)- Clopidogrel bisulfate.
13. The undersigned declares that all statements made herein of my personal knowledge are true and that all statements made on information and belief are believed true; and further that these statements made with the knowledge that any willful false statement are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of this patent application or any patent issuing thereon.

Date: _____

Dr. Bipin Pandey

Fig. 1

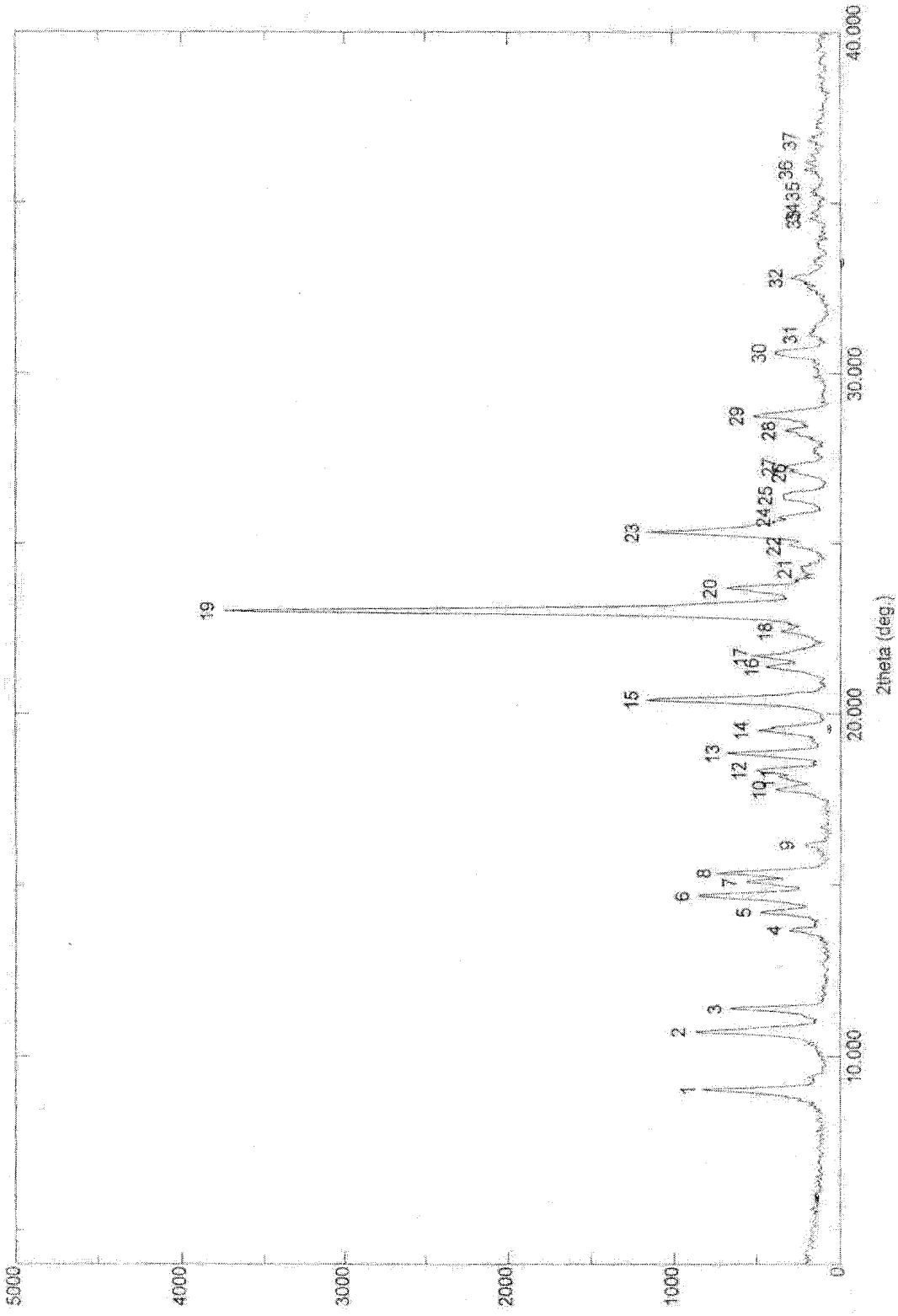
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Fig. 2

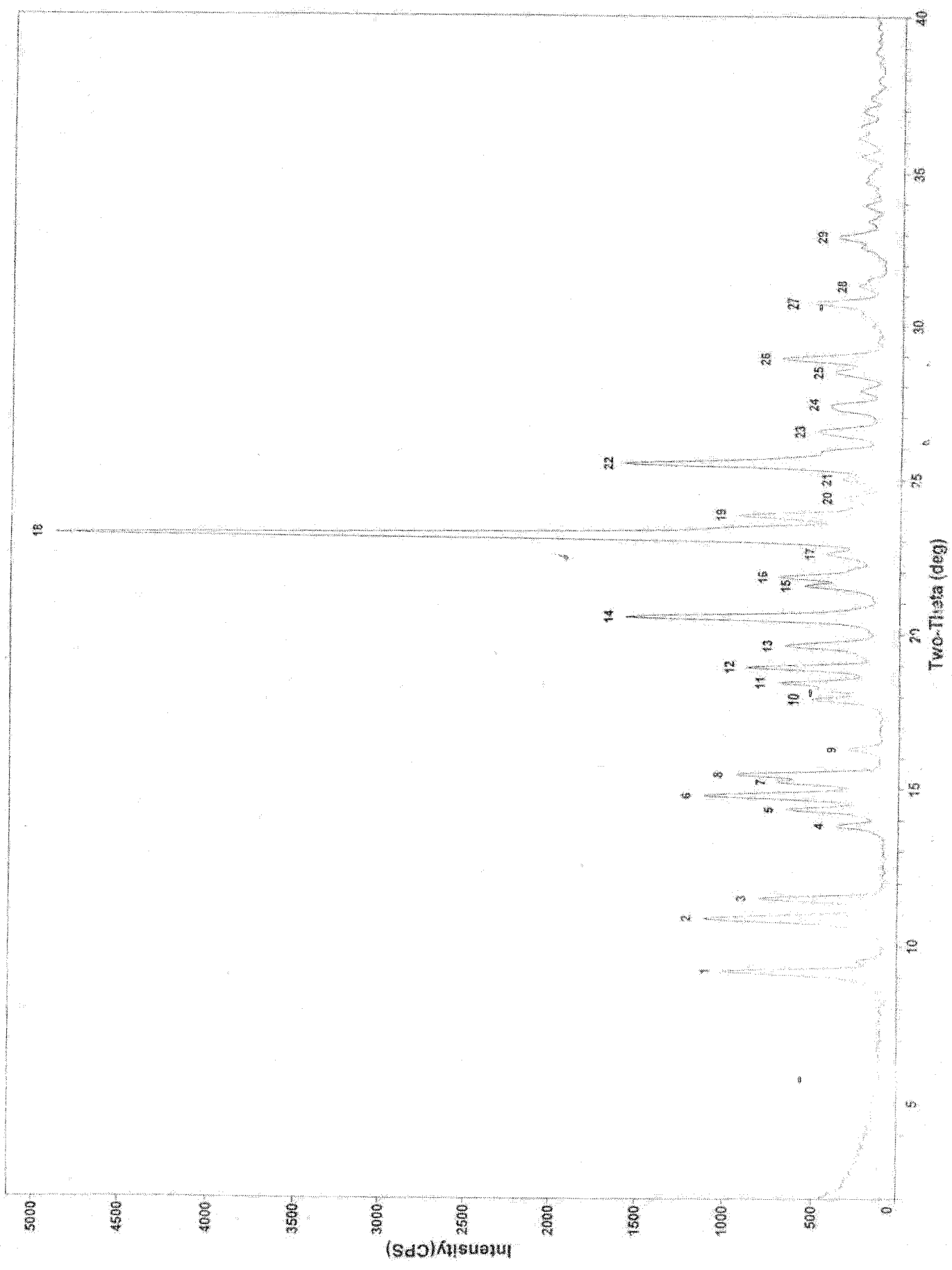

Fig. 3

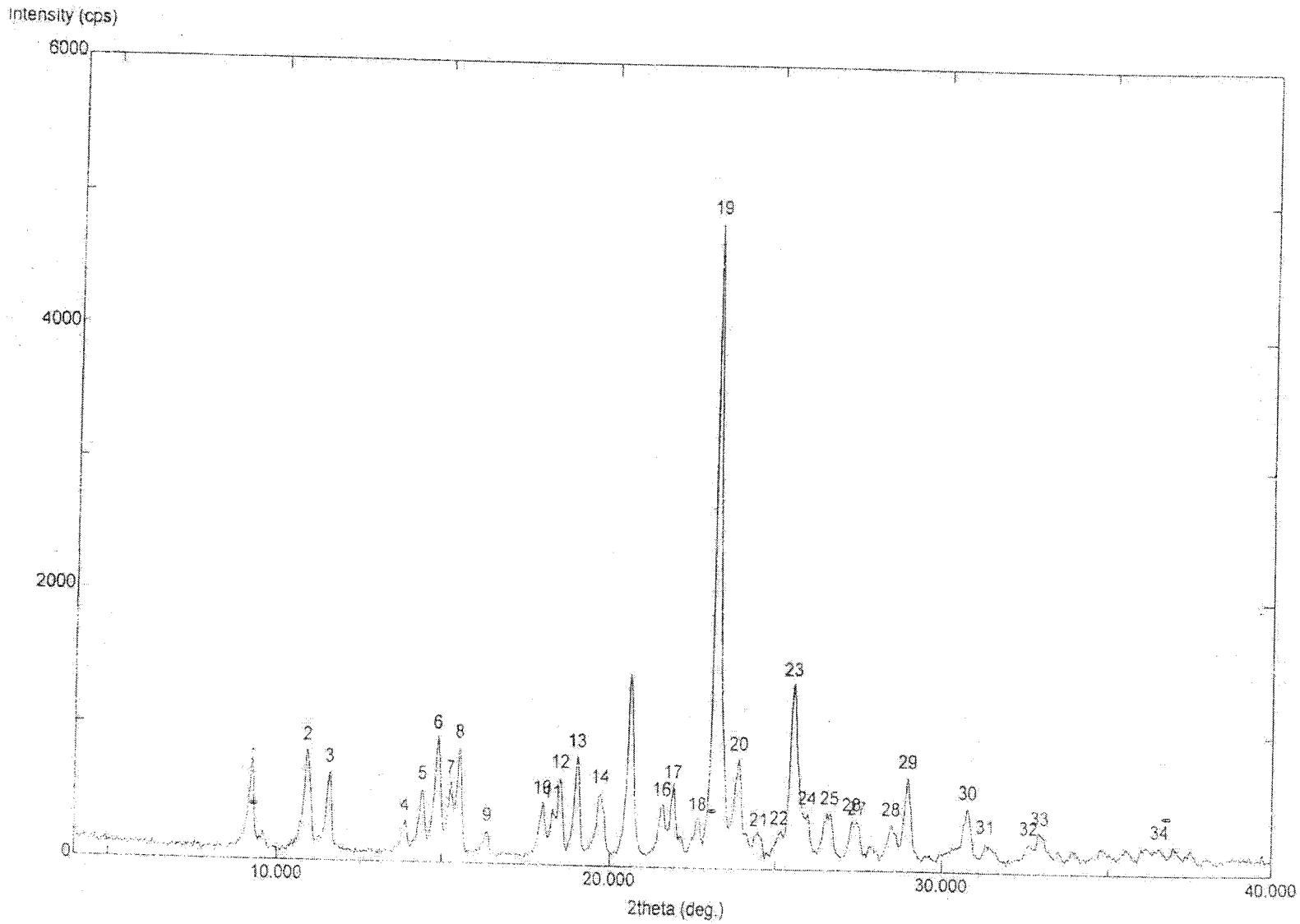
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Fig. 4

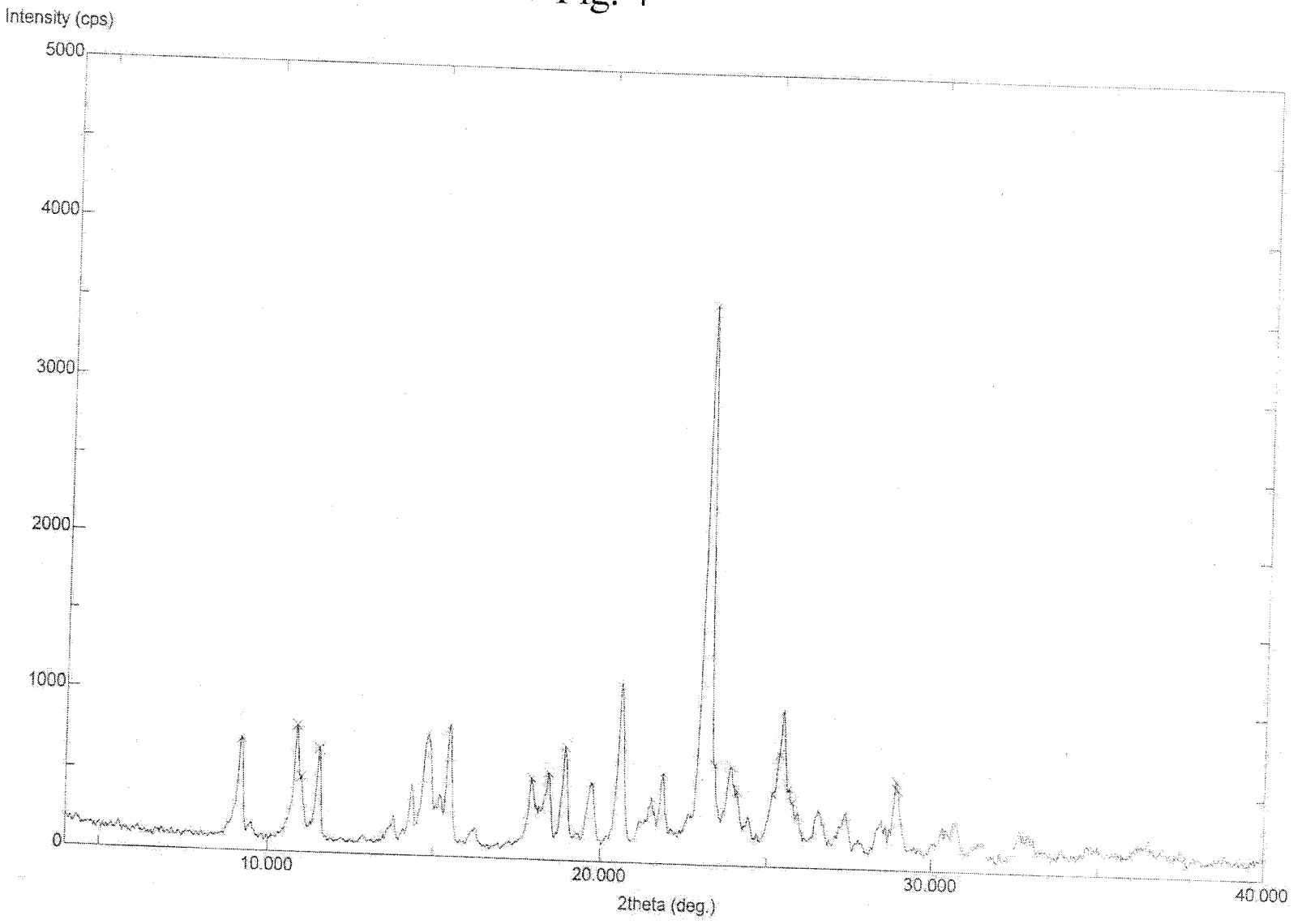
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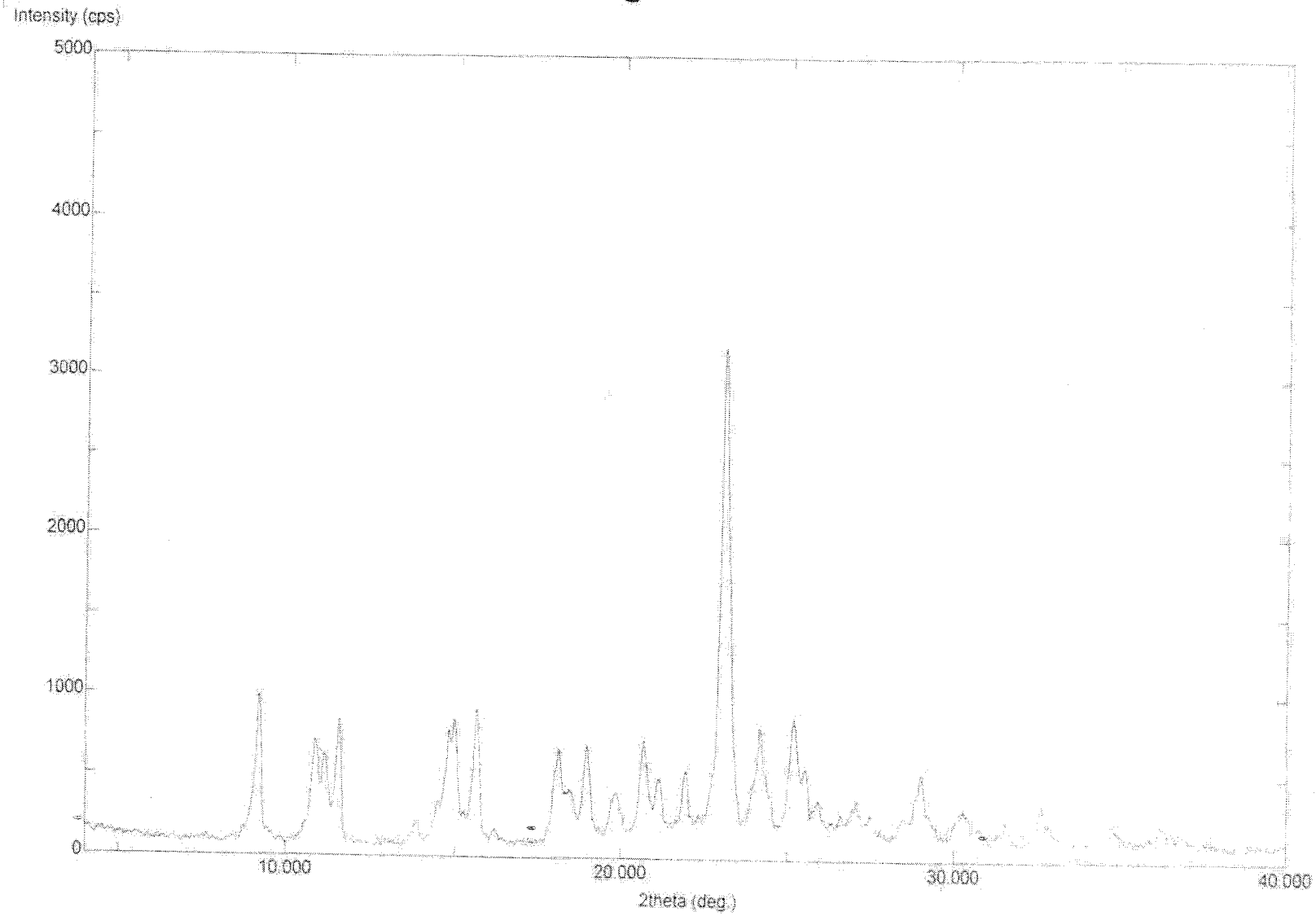
Fig. 5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